

## Thalidomide: Tragic Past and Promising Future

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**T**halidomide ( $\alpha$ -N-[phthalimido] glutarimide) was first synthesized in 1953 by Ciba, a Swiss pharmaceutical firm, and then in 1954 by Kunz, a chemist at Chemie Grünenthal, a German pharmaceutical company.<sup>1,2</sup> On October 1, 1957, Chemie Grünenthal introduced the drug into the market as a sedative.<sup>1,3,4</sup> Thalidomide lacked the typical addictive properties of barbiturates and produced a natural, calm sleep. Furthermore, a median lethal dose ( $LD_{50}$ ) could not be established in rodent models, and death in humans from accidental or intentional overdosing was practically impossible. Thus, thalidomide was believed to be basically nontoxic compared with other available sedatives. By 1960, thalidomide was sold by Chemie Grünenthal and its licensees in more than 40 countries and became popular as both a sedative and a morning sickness treatment during pregnancy. Thalidomide was marketed under various commercial names such as Contergan, Distal, Softenon, Neurosedyn, Isomin, Kedavon, Telargan, and Sedalis.<sup>5</sup>

### TRAGIC PAST

On November 18, 1961, four years after thalidomide entered the market, Widukind Lenz, a German physician and geneticist, indicated that thalidomide was associated with severe teratogenic malformations.<sup>6</sup> He had observed more than 50 malformed infants whose mothers had taken the drug during pregnancy. In December 1961, independent confirmation came from William McBride, an Australian obstetrician, who questioned whether thalidomide was responsible for teratogenic malformations.<sup>6</sup> The findings of these 2 investigators soon were confirmed by numerous physicians worldwide. As a result, by the end of 1961, thalidomide was taken off the market in most countries. Although the manufacturers of thalidomide initially contested these findings, the drug quickly was proved to be a powerful teratogen; nearly 10,000 infants were affected worldwide.

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Fetal malformations due to thalidomide occur when the drug is ingested by a pregnant woman between days 35 and 49 after the last menstrual period. A single pill is sufficient to produce teratogenic effects. Fetal malformations include absence of ears and arms, deafness, phocomelia, defects in the face and palate, and malformations of the gastrointestinal system. Approximately 40% of affected infants die within their first year of life.<sup>3,4</sup>

In the United States, the drug was never approved for marketing, thus averting a major tragedy. Thalidomide initially was denied Food and Drug Administration (FDA) approval by Dr Frances Kelsey, who reviewed the new drug application and had concerns about the lack of safety data.<sup>7</sup> Dr Kelsey was instrumental in preventing the drug from being marketed in the United States. Once the teratogenic properties of the drug were known, the application for FDA approval was withdrawn. Dr Kelsey subsequently received the President's Award for Distinguished Federal Civilian Service from President John F. Kennedy. The thalidomide tragedy led to major reorganization of the FDA; the agency became responsible for approving drug safety and efficacy with the passage of the Kefauver-Harris amendments by Congress in 1962. The words of D. M. Burley, Medical Advisor to the Distiller's Company that marketed thalidomide in England, proved prophetic: "...if the drug can be shown definitely to have teratogenic effects this may have far-reaching consequences in terms of pharmacological testing...."<sup>8</sup>

Today, individuals affected by the thalidomide tragedy have reached adulthood and have adapted to their severe physical challenges. Several organizations for these affected individuals exist, including the Thalidomide Victims Association of Canada ([www.thalidomide.ca](http://www.thalidomide.ca)).

### REINTRODUCTION OF THALIDOMIDE INTO CLINICAL PRACTICE

Shortly after the teratogenic properties of thalidomide became known, astute physicians considered the drug as a possible cancer treatment.<sup>9</sup> They reasoned that a drug powerful enough to cause such severe defects in rapidly growing fetal tissues and organs would probably have similar effects against malignant tumors.<sup>10</sup> In fact, at least 3 large clinical trials involving approximately 200 patients were undertaken in the United States to investigate thalidomide use for treatment of advanced cancer.<sup>11,12</sup> No notable activity was seen with this drug in any of these early trials, and enthusiasm for continuing research of

thalidomide as an anticancer agent disappeared for about 3 decades.

Although thalidomide was taken off the market and was proved unsuccessful in the treatment of cancer, it never disappeared from the field of medicine. In November 1964, Dr Jacob Sheskin, an Israeli physician working in Jerusalem, encountered a 44-year-old man with erythema nodosum leprosum (ENL), a complication of leprosy.<sup>13</sup> The patient had fever, severe muscle and joint pain, and a skin eruption and was unable to sleep. Dr Sheskin prescribed thalidomide as a sedative because he believed there was no contraindication to its use in this setting. However, the patient had an unexpected and dramatic resolution of ENL within 3 days. Withdrawal of thalidomide led to the recurrence of ENL, and reinstitution of the drug led to complete response. Dr Sheskin later confirmed the remarkable activity of thalidomide for ENL in 5 consecutive patients.<sup>13</sup> These findings were confirmed subsequently by other scientists and by a randomized trial undertaken by the World Health Organization.<sup>14</sup> Thalidomide quickly was shown to be one of the most active agents in the treatment of ENL reactions of leprosy.

In 1979, thalidomide was found to have activity in the treatment of Behçet syndrome.<sup>15</sup> In 1988, the drug was shown to be effective for the treatment of graft-versus-host disease.<sup>16-20</sup> However, one of the factors that most helped in the revival of thalidomide was the effectiveness of the drug against the oral ulcers<sup>21</sup> and wasting<sup>22</sup> associated with human immunodeficiency virus (HIV) infection. These findings led to the continued availability of thalidomide as part of compassionate-use or clinical trials. The mechanism of action of thalidomide in these immune-related disorders was unclear. In 1991, Dr Gilla Kaplan and colleagues<sup>23</sup> found that the anti-inflammatory and immunomodulatory properties of thalidomide probably resulted from suppression of tumor necrosis factor  $\alpha$  release. Subsequent studies confirmed these observations.<sup>24</sup>

Once the activity of thalidomide in HIV-related wasting and aphthous ulcers became known, an underground market for thalidomide was established in the United States, involving importation presumably from South America.<sup>25</sup> The drug was procured through "buyers clubs." These activities raised major concerns at the FDA and prompted efforts to make thalidomide legally available on a restricted basis for use in the United States.<sup>26</sup> After a long deliberation period, the FDA approved thalidomide for treatment of ENL in the United States in July 1998. Because leprosy is not prevalent in the United States, this approval can be viewed as one way of providing highly restricted legal access to the drug for other disease conditions including HIV.

Access to thalidomide through restricted FDA approval requires the prescribing physician and the dispens-

ing pharmacy to register with the System for Thalidomide Education and Prescribing Safety (STEPS) program.<sup>27,28</sup> In this program, women of childbearing age must undergo pregnancy testing before starting therapy and every 2 to 4 weeks during treatment. They must abstain from sexual intercourse or use 2 highly effective contraceptive methods during treatment. Men must abstain from sexual intercourse or use a condom during treatment, even if they had undergone a successful vasectomy. All patients must adhere to these measures for at least 1 month after the last dose of the drug. Breastfeeding is contraindicated while taking the drug. Ensuring complete compliance with the STEPS program is important to prevent teratogenicity.<sup>29</sup>

#### ANTIANGIOGENIC PROPERTIES OF THALIDOMIDE AND SUCCESSFUL TREATMENT OF MYELOMA

In 1971, Dr Judah Folkman<sup>30</sup> hypothesized that tumor cells require blood vessels to grow and that tumors could not grow larger than 1 to 2 mm unless they induced angiogenesis (the formation of new blood vessels). Dr Folkman also proposed that antiangiogenic strategies can control tumor growth and can be effective in the treatment of malignancy.<sup>31,32</sup> Researchers in his laboratory isolated potent endogenous antiangiogenic substances such as angiostatin and endostatin that are now in clinical trials for cancer.<sup>33-35</sup> Interest in antiangiogenic agents peaked in the 1990s.<sup>36</sup>

D'Amato et al<sup>37</sup> and Kenyon et al<sup>38</sup> noted that thalidomide possessed substantial antiangiogenic properties in both a rabbit corneal micropocket assay and a mouse corneal model. They hypothesized that thalidomide probably worked by inhibiting the action of vascular endothelial growth factor and basic fibroblast growth factor.

On the basis of evidence that antiangiogenesis was an appropriate target for cancer therapy and given the fact that thalidomide possessed antiangiogenic properties, researchers at the University of Arkansas, headed by Dr Bart Barlogie,<sup>39</sup> treated patients with relapsed and refractory multiple myeloma on a compassionate-use basis with the drug in late 1997. Surprisingly, thalidomide was remarkably effective in these patients, most of whom had no other treatment options. In a clinical trial conducted by these researchers, 32% of 84 patients treated responded to therapy, making thalidomide the first new drug that showed single-agent activity for myeloma in more than 3 decades.<sup>39</sup> These initial studies by the University of Arkansas group were then confirmed by many other centers, including the Mayo Clinic.<sup>40-42</sup> Subsequently, the drug was found to be useful in the early stages of myeloma and is now being tried as a treatment of asymptomatic myeloma and in patients with newly diagnosed disease.<sup>43-47</sup>

Initial studies revealed that in combination with dexamethasone, thalidomide has shown considerable activity in patients with newly diagnosed myeloma.<sup>43,46</sup>

#### THALIDOMIDE IN CURRENT CLINICAL PRACTICE

The most common indication for thalidomide use today is multiple myeloma and related plasma cell disorders. Thalidomide represents a new era in therapy for this incurable and fatal malignancy.<sup>48-50</sup> Because of the availability of other effective therapeutic options, thalidomide is needed much less in the treatment of HIV disease. Over the years, several other promising uses of thalidomide have been discovered,<sup>51,52</sup> including treatment of malignancies such as myelofibrosis with myeloid metaplasia,<sup>53-55</sup> myelodysplastic syndrome,<sup>56,57</sup> Kaposi sarcoma,<sup>58</sup> and renal cell carcinoma.<sup>59-62</sup> The drug also is being studied in nonmalignant conditions including inflammatory bowel disease, reflex sympathetic dystrophy syndrome, and certain autoimmune disorders.

The dosage ranges from 50 to 400 mg/d taken orally at bedtime. The known toxicities of thalidomide include peripheral neuropathy, constipation, fatigue, and sedation.<sup>63</sup> Therapy for myeloma has revealed new and previously unrecognized toxicities of thalidomide, including deep venous thrombosis,<sup>64-67</sup> toxic epidermal necrolysis,<sup>68</sup> and hypothyroidism.<sup>69</sup>

Thalidomide is dispensed as a racemic mixture of dextrorotatory [(R)-] and levorotatory [(S)-] enantiomers.<sup>2,70</sup> Although the (R)- enantiomer is believed responsible for most of the sedative activities of thalidomide and the (S)-enantiomer plays an important role in imparting the teratogenic and antitumor properties, differences in enantiomer selectivity are not clinically relevant because of rapid chiral interconversion in vivo at physiological pH.<sup>71</sup> Therefore, as a result of this rapid racemization, the use of a pure (R)-enantiomer would not have prevented the thalidomide tragedy. Most of the metabolism is by nonenzymatic hydrolysis, and no major dose reductions are needed generally in liver or renal failure.

The mechanism of action of thalidomide is still unclear. Besides inhibition of tumor necrosis factor  $\alpha$  and antiangiogenic properties, the drug affects the immune system by promoting the activity of T cells and natural killer cells.<sup>72-74</sup> It also inhibits the release of various cytokines that are important for tumor cell growth and down-regulates the expression of adhesion molecules that promote binding of tumor cells to the surrounding stromal microenvironment.<sup>75-78</sup> The relatively low activity of thalidomide in in vitro assays and its spontaneous nonenzymatic metabolism in solution to numerous metabolites hamper more definitive studies of its mechanism of action.<sup>70</sup>

#### FUTURE DIRECTIONS

As reflected in Louis Pasteur's statement, "chance favors only the prepared mind,"<sup>79</sup> many discoveries related to the activity of thalidomide in various diseases resulted from chance and involved physicians who were prepared and willing to translate basic scientific findings to their clinical practice. Thalidomide has made a comeback into clinical practice, especially as an anticancer agent. The failure to see an antitumor effect in the 1960s was possibly related to the paucity of patients with myeloma, myelofibrosis, and other thalidomide-responsive cancers in those studies. No notable changes have been made in dosing, schedule, or formulation since the 1960s. Possibly, responding patients were missed in the early studies because of inadequate tools to monitor response.

Current clinical trials are analyzing the role of thalidomide alone and in combination with other active agents in numerous malignancies including multiple myeloma. Nevertheless, given the teratogenic properties of the drug, there is an urgent need to identify analogues of the drug that have similar or better beneficial properties without its teratogenic effects. One such analogue, CC-5013 (lenalidomide), has shown considerable promise in the treatment of relapsed and refractory myeloma and is currently in phase 2 and phase 3 clinical trials.<sup>80-82</sup> The future looks promising for the development of safer analogues, and possibly one day these analogues will replace thalidomide in clinical practice.

Currently, no data exist about whether thalidomide will benefit patients in whom the newer, possibly safer, analogues fail. Given the marked differences in toxicity, it is possible that the mechanism of action of thalidomide in myeloma and other cancers is at least partially different from that of CC-5013 and other analogues. The Eastern Cooperative Oncology Group is developing a clinical trial to evaluate thalidomide in patients with myeloma who do not respond to the new analogue CC-5013. This and other similar trials eventually will determine whether thalidomide will be used as an anticancer agent in the long term or will be pushed into retirement by one or more safer analogues. Until then, thalidomide used in strict compliance with the STEPS program plays a critical role in the therapy for diseases such as multiple myeloma.

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